

**Amendment and Response**

Applicant: Winthrop D. Childers et al.

Serial No.: 10/808,803

Filed: March 25, 2004

Docket No.: 200314139-1

Title: METHOD OF SORTING CELLS IN SERIES

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**REMARKS**

The following remarks are made in response to the Office Action mailed October 23, 2007, in which claims 1-20, 22, 24, 26 and 27 were rejected, and in which the subject matter of claims 21 and 25 was indicated to be allowable if placed in independent form. With this Response, claims 1, 4-6, 11-12, 15-17, 20, 22, and 25 have been amended, claims 9-10, 14, 18-19, 21, 23-24, and 26-27 have been canceled, and 28-29 new claims have been added. Claims 1-8, 11-13, 15-17, 20, 22, 25, and 28-29 are pending in the application and are presented for reconsideration and allowance.

**Objection to the Specification**

Applicants have amended the specification to include the missing serial numbers of the related applications.

**Claim Rejections under 35 U.S.C. § 103**

In the Office Action, claims 1-20, 22-24, 26 and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Talary et al. U.S. Patent 7,169,282 (the Talary Patent) in view of the Quake et al. U.S. Patent 6,964,736 (the Quake Patent).

Applicants have canceled claims 9-10, 14, 18-19, 21, 23-24, and 26-27.

Applicants' independent claim 1 specifies a method of sorting cells. The method comprises, among other things, providing a fluid flow path for moving cells through a series of cell sorters in a first direction with an output of a preceding cell sorter of the series communicating with an input of a successive cell sorter of the series. Within each cell sorter, a first portion of the cells is separated away from a second portion of the cells and toward the output of a respective cell sorter by applying a first temporally varying non-uniform electric field via a first electrode array to cause movement of the first portion of the cells in a second direction across the fluid flow path, the second direction having a component generally transverse to the first direction.

As admitted in the Office Action, the Talary Patent discloses that at least one of electrode arrays is used to trap certain particles, rather than to move or transport them in a

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desired direction so that the cell sorters act as filters. Accordingly, the Talary Patent teaches using the electrode array to stop certain particles while the flow of fluid and other particles is maintained relative to the electrode arrays 201 and out of the filter 110. Later, in a separate step, the trapped particles are released from the electrode arrays 201 and flushed from the filter 110. See, for example, Column 8, lines 5-20 and 33-37. Therefore, the Talary Patent teaches away from Applicants' claim 1 which recites applying a **second temporally varying non-uniform electric field** from the second electrode array to **maintain transport of the first portion** and the second portion **of cells** along the fluid flow path **in the first direction during movement of the first portion of cells across the fluid flow path in the second direction**.

In further sharp contrast to the Talary Patent, Applicants' claim 1 specifies that separating the first portion from the second portion of cells includes **interposing** the fluid flow path (in each cell sorter) between the first electrode array and a second electrode array that is **vertically disposed** relative to the first electrode array.

In this regard, Applicants note that substantially the same limitations were previously presented in claim 6 as originally filed, and that in the Office Action, Figures 7A-7B of the Talary Patent were cited against originally filed claim 6. However, the system described in association with Figures 7A-7B (see Column 15, lines 4-24) of the Talary Patent includes overlapping electrode arrays 910 and 920 disposed over the same area of a substrate. The arrays 910 and 920 are electrically isolated from each other with an insulating layer 930 separating the respective arrays 910 and 920. Because the insulator 930 separates the respective electrode arrays 910, 920, no fluid flow of cells can occur between the respective electrode arrays 910 and 920 of the system in the Talary Patent. Therefore, the Talary Patent teaches away from Applicants' claim 1 in which the fluid flow path is interposed between the first electrode array and the second electrode array.

For at least these reasons, the Talary Patent fails to teach, suggest, or otherwise render obvious Applicants' claim 1.

The Quake Patent fails to cure the deficiencies of the Talary Patent. In particular, the Quake Patent discloses sorting by application of an electric field between a pair of single electrodes 110, 112 across a discrimination region (see, for example, Figure 4A; Column 2, lines 60-67; and Column 8, lines 32-53).

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However, the Quake Patent fails to provide applying a **second** temporally varying non-uniform electric field via a second electrode array (in addition to a first temporally varying non-uniform electric field applied via a first electrode array) to maintain movement of a first portion and a second portion of the cells along the fluid flow path in a first direction during movement of the first portion of cells in a second direction across the fluid flow path (caused by application of a first temporally varying non-uniform electric field) generally transverse to the first direction and away from the second portion of the cells. Instead, in the Quake Patent, the embodiment of Figure 4A employs hydrostatic pressure to move a solution containing particles through the discrimination region (see, for example, Column 13, line 65 – Column 14, line 20), and not a **second** temporally varying non-uniform electric field, as recited in Applicants' claim 1.

Moreover, in another example, the Quake Patent discloses an embodiment of Figure 4B that employs electroosmotic flow to move the particles and solution through the discrimination region (see, for example, Column 14, lines 20-38). However, in this arrangement, the respective electrodes 132 and 134 are not vertically disposed relative to one another and a fluid flow path is not interposed between the respective electrodes 132 and 134. Therefore, the Quake Patent fails to disclose Applicants' claimed feature of the second electrode array being vertically disposed relative to the first electrode array with the fluid flow path interposed therebetween, as recited in Applicants' claim 1.

In addition, the Quake Patent does not disclose applying a **second temporally varying non-uniform electric field from the second electrode array** (in addition to a first temporally varying non-uniform electric field via a first electrode array) to maintain transport of the first portion and the second portion of cells along the fluid flow path, as recited in Applicants' claim 1. Instead, as noted above the examples in the Quake Patent use hydrostatic pressure or simple electroosmotic pressure to move the solution and particles through the discrimination region.

Moreover, the discrimination region D in the Quake Patent is aligned to allow movement only in one direction (e.g., a direction perpendicular to branches 106, 108) during the sorting of the particle between the two branches 106 and 108. Accordingly, the discrimination region does not permit **maintaining transport of the first portion** and the second portion **of cells** along the fluid flow path **in the first direction during movement of**

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**the first portion of cells across the fluid flow path in the second direction**, as recited in Applicants' claim 1.

For at least these reasons, the Quake Patent fails to cure the deficiencies of the Talary Patent regarding Applicants' claim 1.

Accordingly, Applicants respectfully submit that the combination of the Talary Patent and the Quake Patent does not render obvious Applicants' invention defined in independent claim 1.

For at least these reasons, the Talary Patent and the Quake Patent fail to anticipate, teach, suggest, or otherwise render obvious Applicants' independent claim 1. Accordingly, Applicants respectfully submit that independent claim 1 is allowable over the combination of the Talary Patent and the Quake Patent. Claims 2-8 are believed to be allowable based on their dependency from patentably distinct independent claim 1.

Applicants' independent claim 11 specifies a cell sorter system for a biodevice comprising, among other things, a plurality of cell sorters arranged in series including a first cell sorter and a second sorter. Each respective cell sorter includes: (1) a fluid flow mechanism configured to maintain a fluid flow of cells in a first direction from an input to a first flow outlet and to a second flow outlet; and (2) an electrode array configured to apply a temporally varying non-uniform electric field to the cells to move at least one portion of the cells in a second direction having a component generally transverse to the first direction, wherein the first flow outlet the first cell sorter is in communication with the input of the second cell sorter.

Applicants' independent claim 11 further recites an arrangement in which a temporally varying non-uniform electric field is applied in a first cell sorter (in a series) at a first frequency and in a second, subsequent cell sorter at a second frequency. In sharp contrast, and as admitted in the Office Action, neither the Talary Patent nor the Quake Patent disclose applying a temporally varying non-uniform electric field at a different frequency in at least two cell sorters of a series.

Moreover, Applicants' independent claim 11 further specifies that the electrode array of the first cell sorter is configured to apply the temporally varying non-uniform electric field at a first frequency to cause **movement of a first portion and a third portion of the cells** in

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the second direction **away from a second portion of cells until the first portion and the third portion of cells become positioned to enter the first flow outlet** of the first cell sorter **while the fluid flow mechanism is configured to maintain the flow of the respective first and third portions of cells in the first direction for passage into the first flow outlet of the first cell sorter.**

Neither the Talary Patent nor the Quake Patent provide such an arrangement. On the one hand, the Talary Patent traps target particles out of a fluid flow and then later flushes the trapped target particles out of the filter for collection and use, or to a subsequent filter for further filtering. In other words, the filter disclosed in the Talary Patent uses its electrode array to stop the flow of the target particles while letting other particles and fluid keep flowing. Accordingly, the Talary Patent teaches away from using a first frequency to move a first and third portion of cells away from a second portion of cells (in a direction transverse to a direction of fluid flow) **while simultaneously maintaining, via the fluid flow mechanism, the flow of the respective first and third portions of cells in the first direction**, as recited in Applicants' independent claim 11. Because the Quake Patent discloses sorting particles via branches with hydrostatic pressure (Figure 4A) or electroosmotic pressure (Figure 4B) instead of trapping particles, and trapping particles is the opposite of maintaining a flow of a target particle, the operation of the branch separation mechanism of the Quake Patent is incompatible with the trapping mechanism of the Talary Patent. Accordingly, one of ordinary skill in the art would not attempt to combine the system of the Talary Patent with the Quake Patent.

Moreover, to the extent that the Quake Patent discloses a cascading arrangement and one skilled in the art were to apply that arrangement to the Talary Patent in an attempt to arrive at the system recited in Applicants' claim 11, the result would be a series of stopping stations at which a target particle is stopped and then later released to the next unit in the cascade, and as such, a flow of the target particles would not be maintained.

In further sharp contrast, neither the Talary Patent nor the Quake Patent teaches or suggests the additional feature recited in Applicants' independent claim 11 that in the first cell sorter, both a first portion and a third portion of cells (not just one portion or one target) are moved (via the temporally varying electric non-uniform field) away from the second portion of cells.

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For substantially the same reasons presented in association **with the first cell sorter** of Applicants' independent claim 11, the combination of the Talary Patent and the Quake Patent also fails to disclose that **the electrode array of the second cell sorter** is configured to apply the temporally varying non-uniform electric field at a second frequency to cause movement of the first portion of the cells in the second direction away from the third portion of cells until the first portion of cells become positioned to enter the first flow outlet of the second cell sorter while the fluid flow mechanism is configured to maintain the flow of the respective first portion of the cells in the first direction for passage into the first flow outlet of the second cell sorter, as recited in Applicants' independent claim 11.

Among other distortions, neither the Talary Patent nor the Quake Patent teaches or suggests a system in which the each cell sorter (e.g., first cell sorter, second cell sorter) removes a different type of cells (e.g., the second portion is removed in the first cell sorter, and the third portion is removed in the second cell sorter) and in which the flow of the target particles is maintained, as provided by the invention defined in Applicants' independent claim 11. Accordingly, Applicants respectfully submit that the combination of the Talary Patent and the Quake Patent does not render obvious Applicants' invention as defined in independent claim 11.

For at least these reasons, the Talary Patent and the Quake Patent fail to anticipate, teach, suggest, or otherwise render obvious Applicants' independent claim 11. Accordingly, Applicants respectfully submit that independent claim 11 is allowable over the combination of the Talary Patent and the Quake Patent. Claims 12-13 and 15-16 are believed to be allowable based on their dependency from patentably distinct independent claim 11.

Applicants' independent claim 17 specifies a cell sorter system comprising, among other things, an electrode arrangement including a first electrode array and a second electrode array with the first electrode array configured to apply a first temporally varying non-uniform electric field for causing movement of a field-responsive portion of the cells in a second direction having a component generally transverse to a first direction and the second electrode array configured to apply a second temporally varying non-uniform electric field for causing transport of the cells along a fluid flow path in the first direction.

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For substantially the same reasons presented for the patentability of Applicants' independent claim 1, it is submitted that the combination of the Talary and Quake Patents fails to render obvious Applicants' independent claim 17. More particularly, as previously explained in association with Applicants' independent claim 1, Applicants submit that the arrangement in the Talary Patent of having an insulator 930 arranged between electrode arrays 910, 290 teaches away from an arrangement in which a first electrode array (applying a first temporally varying non-uniform electric field) and the second electrode array (applying a first temporally varying non-uniform electric field) are vertically disposed relative to one another on opposite sides of the fluid flow path with the fluid flow path interposed therebetween, as recited in Applicants' independent claim 17. As previously presented in association with Applicants' independent claim 1, the Quake Patent fails to cure the deficiencies of the Talary Patent.

Accordingly, it is submitted that the combination of the Talary Patent and the Quake Patent does not render obvious Applicants' invention as defined in independent claim 17.

For at least these reasons, the Talary Patent and the Quake Patent fail to anticipate, teach, suggest, or otherwise render obvious Applicants' independent claim 17. Accordingly, Applicants respectfully submit that independent claim 17 is allowable over the combination of the Talary Patent and the Quake Patent.

Applicants' independent claim 22 specifies a cell sorter system for a biodevice comprising a plurality of cell sorters arranged in series. Each cell sorter includes a fluid flow pathway, an electrode arrangement, and a cell diverter. The fluid flow pathway includes a first end and a second end, and is configured for directing a flow of cells in a first direction from the first end to the second end wherein the cells include a first portion and a second portion. The electrode arrangement includes a first electrode structure and a second electrode structure, and is configured for causing movement of the first portion of the cells in a second direction generally transverse to the first direction by successive discrete movements of the first portion of the cells in the second direction. The cell diverter is disposed within, and adjacent to the second end of, the fluid flow pathway to encourage further separation of the first portion of the cells, that have been moved in the second direction, away from the second portion of the cells.

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As cited in the Office Action, the Talary Patent teaches one system including overlapping electrode arrays 910 and 920 disposed over the same area of a substrate. The arrays 910 and 920 are electrically isolated from each other with an insulating layer 930 separating the respective arrays 910 and 920. For example, see Figures 7A and 7B and Column 15, lines 4-24.

In sharp contrast, in Applicants' claim 22, a first electrode structure is on a first side of a fluid flow pathway and a second electrode structure is on a second side of the fluid flow pathway so that the fluid flow pathway is interposed between the first electrode structure and the second electrode structure. However, in the Talary Patent, because insulator 930 separates the respective electrode arrays 910, 920, no fluid flow of cells can occur between the respective electrode arrays 910 and 920 of the system.

In further sharp contrast to the Talary Patent, Applicants' claim 22 recites that the first electrode structure includes an array of generally parallel, spaced apart electrode elements arranged in series **along a first side** of the fluid flow pathway, wherein a longitudinal axis of each electrode element extends across the fluid flow pathway perpendicular to the first direction, and further wherein **a length of the respective electrode elements increases successively from the first end to the second end of the fluid flow pathway**. It is submitted that the Talary Patent teaches away from this feature of Applicants' claim 22 because in the Talary Patent the elements of the electrode array 910 are all the same size while the elements of the electrode array 920 are all the same size.

In further sharp contrast to the Applicants' claim 22, the Talary Patent discloses the application of traveling wave signals to each array such that the respective electrode arrays operate independently of each other (see, for example, Column 15) and that insulator 930, not a fluid flow pathway, is positioned between the respective electrode arrays. Therefore, the Talary Patent teaches away from an arrangement in which the first electrode structure is configured to apply a plurality of **separate non-uniform electric fields** successively one at a time from the first end to the second end of the fluid flow pathway via each separate non-uniform electric field **being applied across the fluid flow pathway from each one of the respective electrode elements of the first electrode structure to the second electrode structure**, as recited in Applicants' claim 22.



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The Quake Patent fails to cure the deficiencies of the Talary Patent. In particular, while the Quake Patent teaches sorting by application of an electric field between a pair of single electrodes 110, 112 across a discrimination region (see, for example, Figure 4A; Column 2, lines 60-67; and Column 8, lines 32-53), the Quake Patent fails to teach or suggest an electrode arrangement configured for causing movement of the first portion of the cells in a second direction generally transverse to the first direction (and away from the second portion of the cells) by successive discrete movements of the first portion of the cells in the second direction, wherein the first electrode structure includes **an array of generally parallel, spaced apart electrode elements arranged in series along a first side** of the fluid flow pathway, wherein a longitudinal axis of each electrode element extends across the fluid flow pathway perpendicular to the first direction, as recited in Applicants' claim 22.

Moreover, because the Quake Patent discloses only the single electrodes 110, 112 in the discrimination region, the Quake Patent also fails to teach or suggest that: **(A) a length of the respective electrode elements increases successively from the first end to the second end of the fluid flow pathway; OR (B) the first electrode structure is configured to apply a plurality of separate non-uniform electric fields successively one at a time from the first end to the second end of the fluid flow pathway via each separate non-uniform electric field being applied across the fluid flow pathway from each one of the respective electrode elements of the first electrode structure to the second electrode structure**, as recited in Applicants' claim 22.

With these deficiencies of the Quake Patent in mind, Applicants respectfully submit that the combination of the Talary Patent and the Quake Patent does not render obvious Applicants' invention as defined in independent claim 22.

For at least these reasons, the Talary Patent and the Quake Patent fail to anticipate, teach, suggest, or otherwise render obvious Applicants' independent claim 22. Accordingly, Applicants respectfully submit that independent claim 22 is allowable over the combination of the Talary Patent and the Quake Patent. Claim 25 is believed to be allowable based on its dependency from patentably distinct independent claim 22.

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In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-20, 22-24, and 26-27 under 35 U.S.C. § 103.

**Allowable Subject Matter**

In the Office Action, claims 21 and 25 were objected to for being dependent upon a rejected base claim, but were indicated to be allowable if rewritten in independent form including all limitations of the base claim and any intervening claims.

Accordingly, Applicants have presented the subject matter of objected to claims 21 and 25 in allowable independent form as new claims 28 and 29, respectively. Allowance of claims 28 and 29 are respectfully requested.

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**CONCLUSION**

In view of the above, Applicants respectfully submit that pending claims 1-8, 11-13, 15-17, 20, 22, 25, and 28-29 are in form for allowance and are not taught or suggested by the cited references. Therefore, reconsideration and withdrawal of the rejections and allowance of claims 1-8, 11-13, 15-17, 20, 22, 25, and 28-29 is respectfully requested.

Applicants hereby authorize the Commissioner for Patents to charge Deposit Account No. 08-2025 the amount of \$210.00 to cover fees as set forth under 37 C.F.R. 1.16(h)(i).

The Examiner is invited to contact the Applicants' representative at the below-listed telephone numbers to facilitate prosecution of this application.

Any inquiry regarding this Amendment and Response should be directed to either Julia Church Dierker at Telephone No. (248) 649-9900, Facsimile No. (248) 649-9922 or Paul S. Grunzweig at Telephone No. (612) 767-2504, Facsimile No. (612) 573-2005. In addition, all correspondence should continue to be directed to the following address:

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Respectfully submitted,

Winthrop D. Childers et al.

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